JML Ling 凌美麟
EW Chan 陳維智
AF Cheng 鄭勳斌

Surveillance of antibiotic resistance in the community: an approach to reducing bacterial resistance to antimicrobial agents

Key Messages

1. Antibiotic resistance is on the rise.
2. Fluoroquinolone resistance was relatively high in organisms causing urinary tract infection.
3. Penicillin resistance in pneumococci was alarming, nonetheless *Streptococcus pneumoniae* had 0% resistance to ampicillin.
4. Group A β-haemolytic streptococci had 0% resistance to penicillin.
5. Frequent surveillance studies are warranted to monitor levels of resistance in the community.

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Department of Microbiology, The Chinese University of Hong Kong
JML Ling, EW Chan, AF Cheng

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Principal applicant and corresponding author:
Dr Julia ML Ling
Department of Microbiology, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China
Tel: (852) 2632 2351
Fax: (852) 2647 3227
E-mail: meilunling@cuhk.edu.hk

Introduction

Antibiotics are frequently prescribed in hospital and general practice. However, they are often given before the culture and sensitivity results of the pathogens have been confirmed. As the distribution of causative organisms and bacterial resistance rates vary in time and place, recent local data are imperative for guiding clinicians' best choice of treatment. Data from different geographical regions provide important information on the epidemiology of pathogens and antibiotic resistance.

Local susceptibility reports are usually based on hospital isolates; reports on susceptibility in community-acquired organisms are few,[1,2] and there is only one on the susceptibility patterns of general practice organisms in Hong Kong.[3] In fact, the need for such data in general practice may be greater, as specimens are often not submitted for culture by general practitioners (GPs).

We aimed to investigate prospectively the characteristics of culture-positive infections of patients visiting GPs throughout Hong Kong.

Methods

This study was conducted from April 2000 to April 2002. General practitioners with clinics in shopping arcades or on the ground floors of commercial buildings were invited to participate. Specimens were taken from patients considered to have a diagnosis of infection and were then collected by laboratory staff and cultured in the microbiology laboratory using standard methods.[4] Organisms isolated were identified and antimicrobial susceptibilities determined by the disc diffusion test.[4] Culture and sensitivity results were sent to the requesting doctors as soon as they became available. Cumulative results on the distribution of organisms and their antimicrobial susceptibilities were produced monthly. Only single-patient isolates were used in the calculation. Isolates were stored for determination of minimal inhibitory concentration (MIC) by an agar dilution method of antibiotics recommended for different organisms by the National Committee for Clinical Laboratory Standards (NCCLS).[5] Strains were considered to be resistant if the MICs were greater than the concentration of antibiotic that inhibits susceptible strains according to the NCCLS.[5] Isolates that were resistant to antibiotics were studied for resistance mechanisms and molecular epidemiology.

Results

Eighty-nine GPs (response rate, 10%) participated in the study. A total of 4741 specimens collected from 3977 patients were sent by these doctors from July 2000 to October 2001. The male to female ratio was 1:1.23 and the 20 to 49 years age-group constituted more than 50% of all patients. The most common specimens were throat swabs (33%), urine (26%), and sputum (16%). The mean culture positive rate was 28%. Detailed results were published in 2003.[6]

Of the 1371 single-patient isolates, 50% were Gram-negative bacteria and 41% were Gram-positive bacteria. The most common organism was *Escherichia coli* (18%), followed by β-haemolytic streptococci (15%), and *Staphylococcus aureus* (12%).[6]

The majority of *E coli* strains were isolated from urine (84%).[6] More than 90% of β-haemolytic streptococci were from throat swabs. Thirty-one percent of *S aureus* isolates were from pus or wounds, while 23 to 24% were from throat and miscellaneous specimens. *Haemophilus influenzae* was mainly isolated from sputum (85%) while other Gram-negatives such as *Pseudomonas aeruginosa*, enterobacters, klebsiellae, and acinetobacters were also mainly isolated from respiratory specimens (56-83%). Forty-seven isolates of *Neisseria gonorrhoeae* were obtained and all except two were from male patients.

More than 60% of *E coli* isolates were resistant to ampicillin but only 16% were resistant in the presence of clavulanic acid.[6] More than 50% were resistant to 4 mg/L cefuroxime but less than 5% to the third-generation cephalosporins ceftriaxone or cefotaxime and none to ceftazidime or imipenem. Thirty percent were resistant to gentamicin, 2% to netilmicin, and none to amikacin. Although 50% were resistant to nalidixic acid, only 22% were resistant to the fluoroquinolones. More than 40% were resistant to the other antibiotics such as trimethoprim, sulfamethoxazole, chloramphenicol, or tetracycline. Significantly more *E coli* isolates were resistant to cefuroxime ($P<0.01$), gentamicin, nalidixic acid, and ofloxacin ($P<0.05$) in this study than our previous study.[3]

About 40% of *H influenzae* were resistant to ampicillin but only 2% were resistant in the presence of clavulanic acid.[6] Forty-seven percent were resistant to cefaclor and 11% and 19% to chloramphenicol and tetracycline, respectively. All were resistant to erythromycin and 69% to clarithromycin. None was resistant to ceftazidime, although 2 to 3% were resistant to the second- and third-generation cephalosporins and fluoroquinolones. Significantly fewer strains were resistant to ampicillin than the previous study ($P<0.01$).[3]

All the 47 isolates of *N gonorrhoeae* were resistant to penicillin and more than 90% to tetracycline, ciprofloxacin, or ofloxacin.[6] However, none was resistant to ceftriaxone and 15% were resistant to spectinomycin.

Three (2%) strains of *S aureus* were resistant to methicillin.[6] Resistance to aminoglycosides (0-5%) or fluoroquinolones (2%) was low. None was resistant to vancomycin. More than 80% of *Streptococcus pneumoniae* were resistant to 0.06 mg/L penicillin, all of which had MICs of 0.12-0.25 mg/L. Resistance to clarithromycin, erythromycin, or tetracycline was high (90%), but none was resistant to ampicillin, cefotaxime, or ceftriaxone. Although 10% of β-haemolytic streptococci were resistant to penicillin, all belonged to groups C and G. Six percent were resistant to ofloxacin. However, resistance to clarithromycin was high (33%). None of the enterococci were resistant to 8 mg/L penicillin or ampicillin and vancomycin and less than 10% (4-9%) were resistant to fluoroquinolones.

Beta-lactam resistance in 162 strains of *E coli* was due to production of β-lactamases of 12 different isoelectric points (pI) ranging from 5.1 to 8.0. Fifty-seven percent of strains produced a β-lactamase of pI 5.4, 19% produced a β-lactamase of pI 5.2, and 1-4% produced a β-lactamase of 10 other pIs. Ampicillin-resistance in klebsiellae was due to production of β-lactamases of 12 different pIs ranging from 7.2 to 8.3 with 59% producing a β-lactamase of pI 7.6, 9% pI 7.8 and 2-6% produced a β-lactamase of the other pIs.

Deoxyribonucleic acid (DNA) sequencing of the quinolone resistance determining region of *gyrA*, *gyrB*, *parC*, and *parE* of 57 strains of *E coli* that were resistant to 0.12 mg/L of ciprofloxacin or ofloxacin showed that gene mutations were present in the *gyrA* gene leading to Ser83->Leu and Asp87->Asn or Asp87->Tyr; *parC* leading to Ser58->Ile and *parE* leading to Ser458->Ala. No mutation was detected in the *gyrB* gene. Pulsed-field gel electrophoresis analysis of total DNA from resistant strains showed that all strains had <90% similarity.[4]

Discussion

This study was initiated to provide up-to-date information on the distribution and antimicrobial susceptibilities of community-acquired organisms. Eighty-nine practising community doctors volunteered to provide appropriate specimens of patients in whom they had diagnosed infections according to specified guidelines.[4] The specimens were collected by laboratory staff within the same or the next day and cultured in the laboratory. The age distribution of patients was similar to the Hong Kong population with the majority being within the 20-49 years age-group. This data collection was quite representative of community-acquired infections in Hong Kong.

Throat swabs and sputa constituted 49% of all specimens, while one-quarter (26%) of specimens were from urine. This is comparable to our previous study, which yielded 48% and 28%, respectively.[3] The large number of urine samples collected was likely to be related to the larger proportion of women than men in the study population (male:female ratio=1:1.23).Urinary tract infections are more common in women.

Due to the large numbers of throat swabs and urine samples collected, it was not surprising to find β-haemolytic streptococci and *E coli* as the principal organisms isolated. However, this was in contrast to the observations in a previous study, where *H influenzae* was the most common organism isolated, with *E coli* and β-haemolytic streptococci the third and seventh most common, respectively.[3] The small number of *H influenzae* strains isolated in this study indicates that chest infections caused by this organism have decreased in importance. In the previous study, 13% of sputa yielded *H influenzae* while only 9% yielded the organism in this study.[3] The isolation of enterobacter and non-enterobacteria such as *P aeruginosa* and acinetobacters from respiratory specimens probably represented colonisation rather than true pathogens. The comparatively large numbers of *N gonorrhoeae* isolated from urethral swabs indicate a rising incidence of gonorrhoea in the community.

Penicillin-resistance in *S pneumoniae* was observed in 81% of samples, representing a five-fold increase since 1993,[3] although the organism was mainly isolated from respiratory specimens and the resistance was of low-level (MICs <1 mg/L). The third-generation cephalosporins remained effective against this organism.

Ampicillin-resistance remained at 60 to 70% in *E coli*. However, fluoroquinolone-resistance increased considerably, from 6% resistance to ofloxacin to 22% and from 0% to 18% in *Proteus* and *Morganella*, the organisms commonly causing urinary tract infection.[3] Whether this was related to the frequent prescription of fluoroquinolones for treatment of this infection requires further investigation. Although resistance to the third-generation cephalosporins was not a problem in the Gram-negatives, these mainly intravenous drugs were usually not chosen for treating community-acquired infections.

It is surprising to find a significant decrease in ampicillin resistance in *H influenzae* (from 64% to 39%, $P<0.01$).[3] However, resistance to macrolides remained high, even to clarithromycin (69%). Second- and third-generation cephalosporins and the fluoroquinolones remained effective (≤3% resistance).

There were three strains of methicillin-resistant *S aureus* (MRSA), indicating that MRSA is not only a hospital phenomenon.

Although 10% of β-haemolytic streptococci were resistant to penicillin, all were non–group A. The newer fluoroquinolones are probably the drugs of choice rather than the macrolides for infections caused by this group of organisms.

Penicillin is no longer effective for treating gonorrhoea. With the considerably high level of resistance to fluoroquinolones (>30%) and spectinomycin (15%), ceftriaxone is the drug of choice for those tested in this study.

Ampicillin resistance in *E coli* was due to production of β-lactamases of pIs ranging from 5.1 to 8.0—similar to those of hospital strains,[7] while fluoroquinolone resistance in *E coli* was due to mutations in the *gyrA*, *parC*, and *parE* gene. Ampicillin resistance in klebsiellae was due to production of β-lactamases of pIs ranging from 7.2 to 8.3. However, since β-lactamases produced by this organism and target gene mutations leading to fluoroquinolone resistance in *E coli* have not been reported previously in Hong Kong, we could not compare results with hospital isolates.

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References

1. Ling JM, Cheng AF. Antimicrobial resistance of clinical isolates from 1987 to 1993 in Hong Kong. Hong Kong Med J 1995;1:212-8.
2. Ling JM, Ng TK, Cheng AF, Norrby SR. Susceptibilities to 23 antimicrobial agents and beta-lactamase production of blood culture isolates of *Acinetobacter* sp in Hong Kong. Scand J Infect Dis Suppl 1996;101:21-5.
3. Ling JM, Lam AW, Cheng AF. Bacteriology and antimicrobial susceptibilities of community-acquired infections. Hong Kong Pract 1993;15:2653-62.
4. Murray PR. Manual of clinical microbiology. 7th ed. Washington, DC: ASM Press; 1999.
5. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 4th ed. Approved standards M7-A4. Wayne, Pa: National Committee for Clinical Laboratory Standards; 1997.
6. Ling JM, Lam AW, Chan EW, Cheng AF. What have we learnt from community-acquired infections in Hong Kong? J Antimicrob Chemother 2003;51:895-904.
7. Ling TK, Lyon DJ, Cheng AF, French GL. In-vitro antimicrobial susceptibility and beta-lactamases of ampicillin-resistant *Escherichia coli* in Hong Kong. J Antimicrob Chemother 1994;34:65-71.